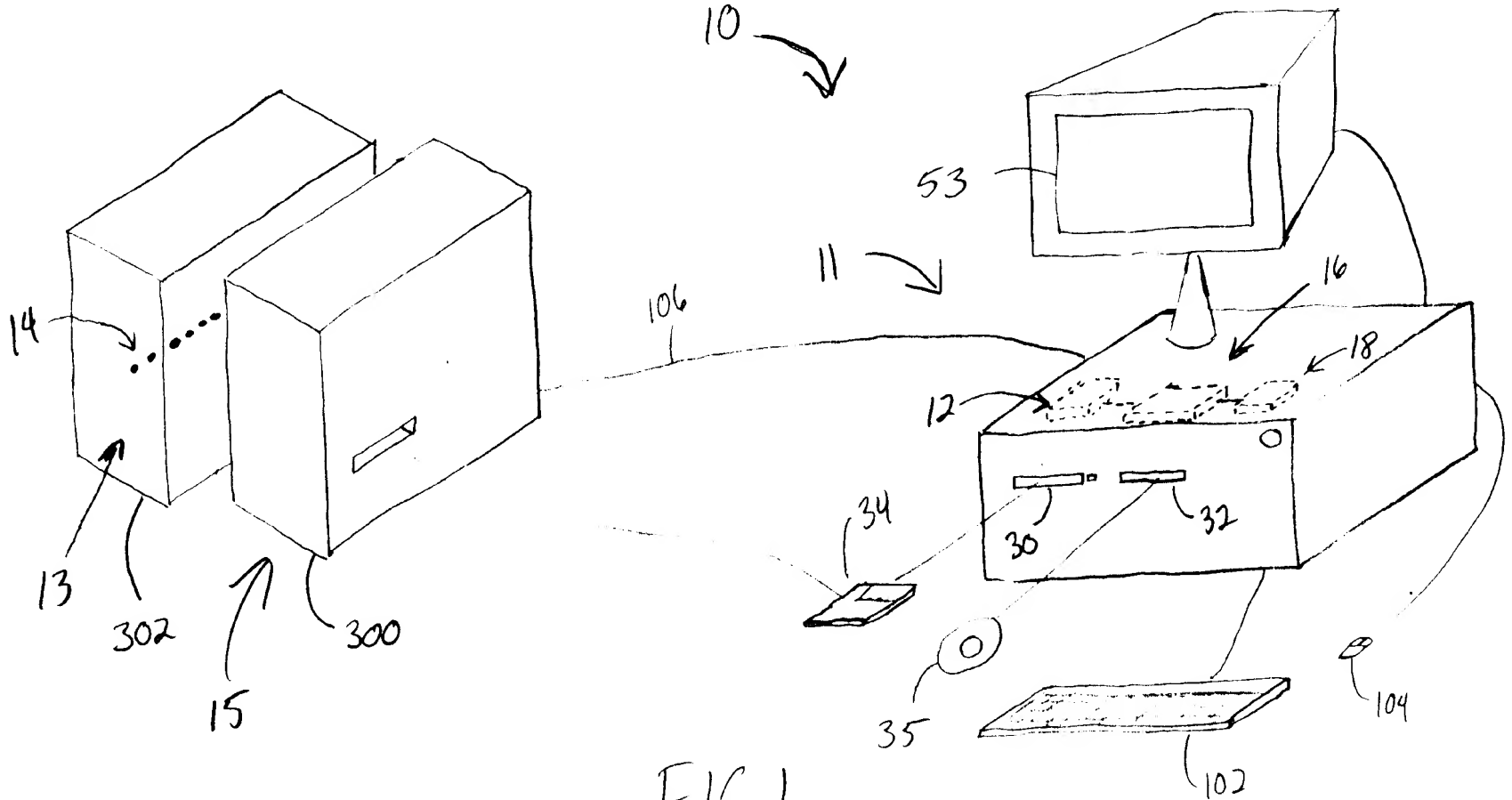


FIG. 1

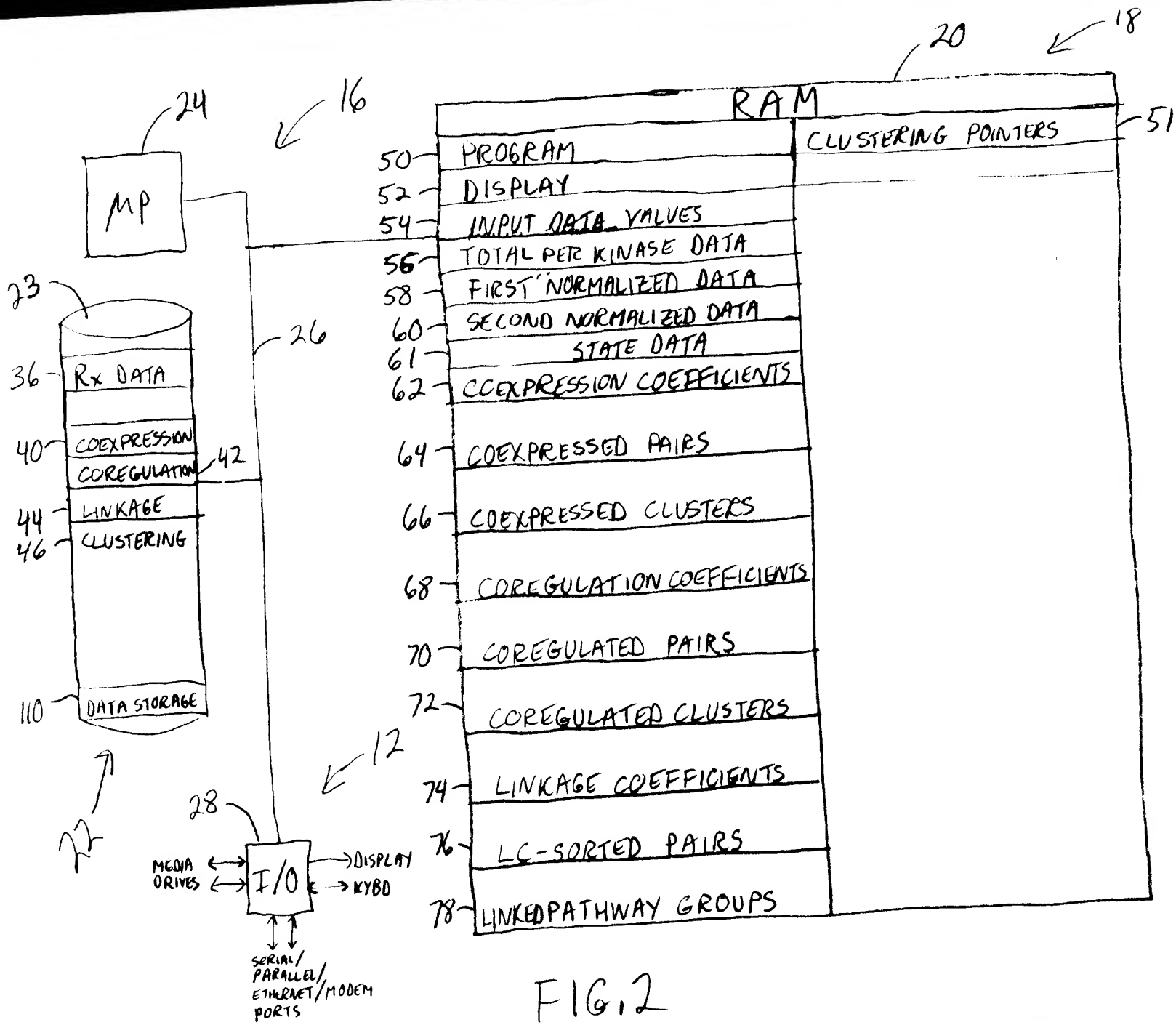

18
20
RAM
CLUSTERING POINTERS
51
24
16
MP
23
26
50 PROGRAM
52 DISPLAY
54 INPUT DATA VALUES
56 TOTAL PER KINASE DATA
58 FIRST NORMALIZED DATA
60 SECOND NORMALIZED DATA
61 STATE DATA
62 COEXPRESSION COEFFICIENTS
64 COEXPRESSED PAIRS
66 COEXPRESSED CLUSTERS
68 COREGULATION COEFFICIENTS
70 COREGULATED PAIRS
72 COREGULATED CLUSTERS
74 LINKAGE COEFFICIENTS
76 LC-SORTED PAIRS
78 LINKED PATHWAY GROUPS
36 Rx DATA
40 COEXPRESSION
COREGULATION
42
44 LINKAGE
46 CLUSTERING
110 DATA STORAGE
12
28
MEDIA DRIVES
I/O
DISPLAY
KYBD
SERIAL/ PARALLEL/ ETHERNET/MODEM PORTS

FIG. 2

RECEIVE ROUTINE

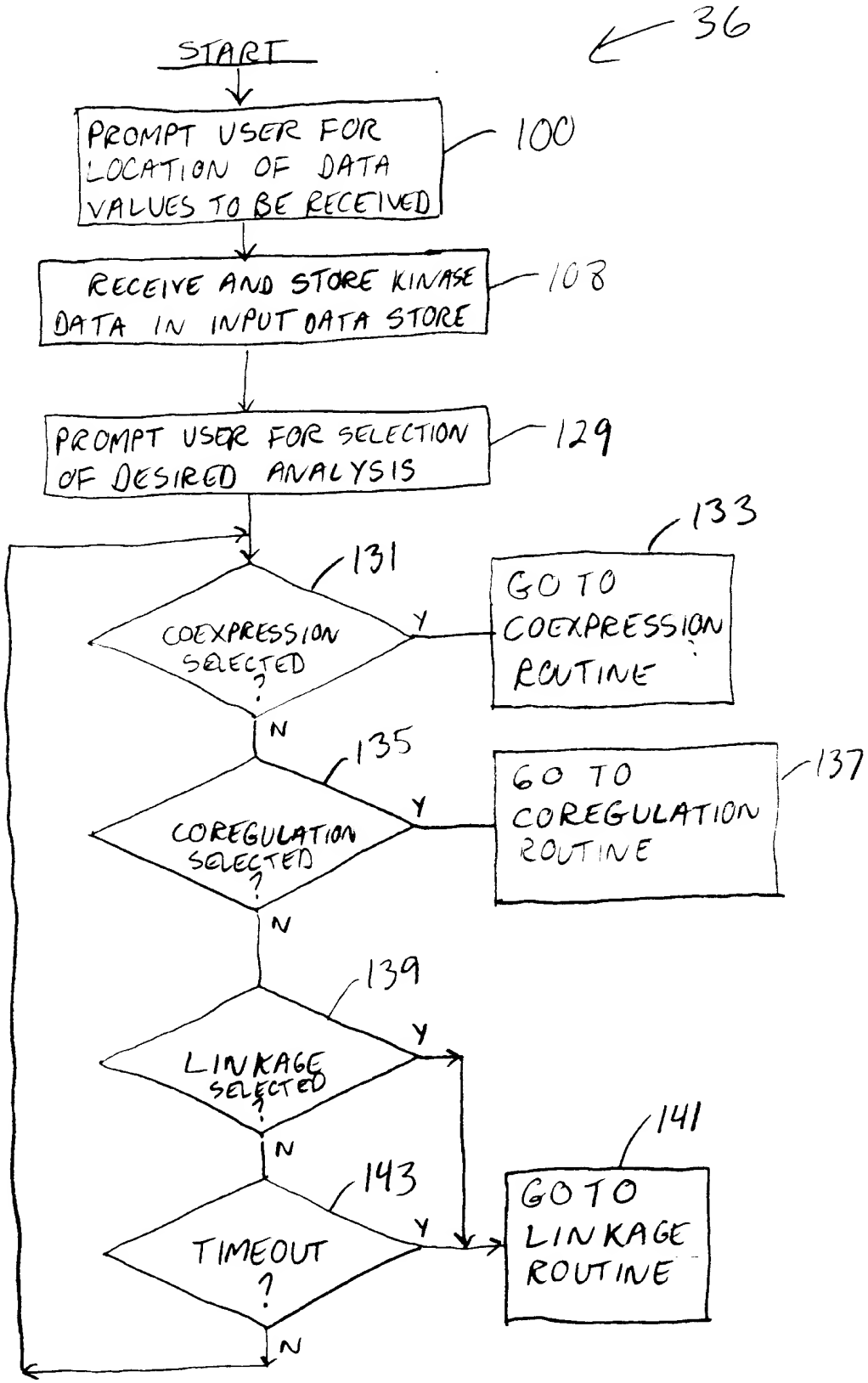
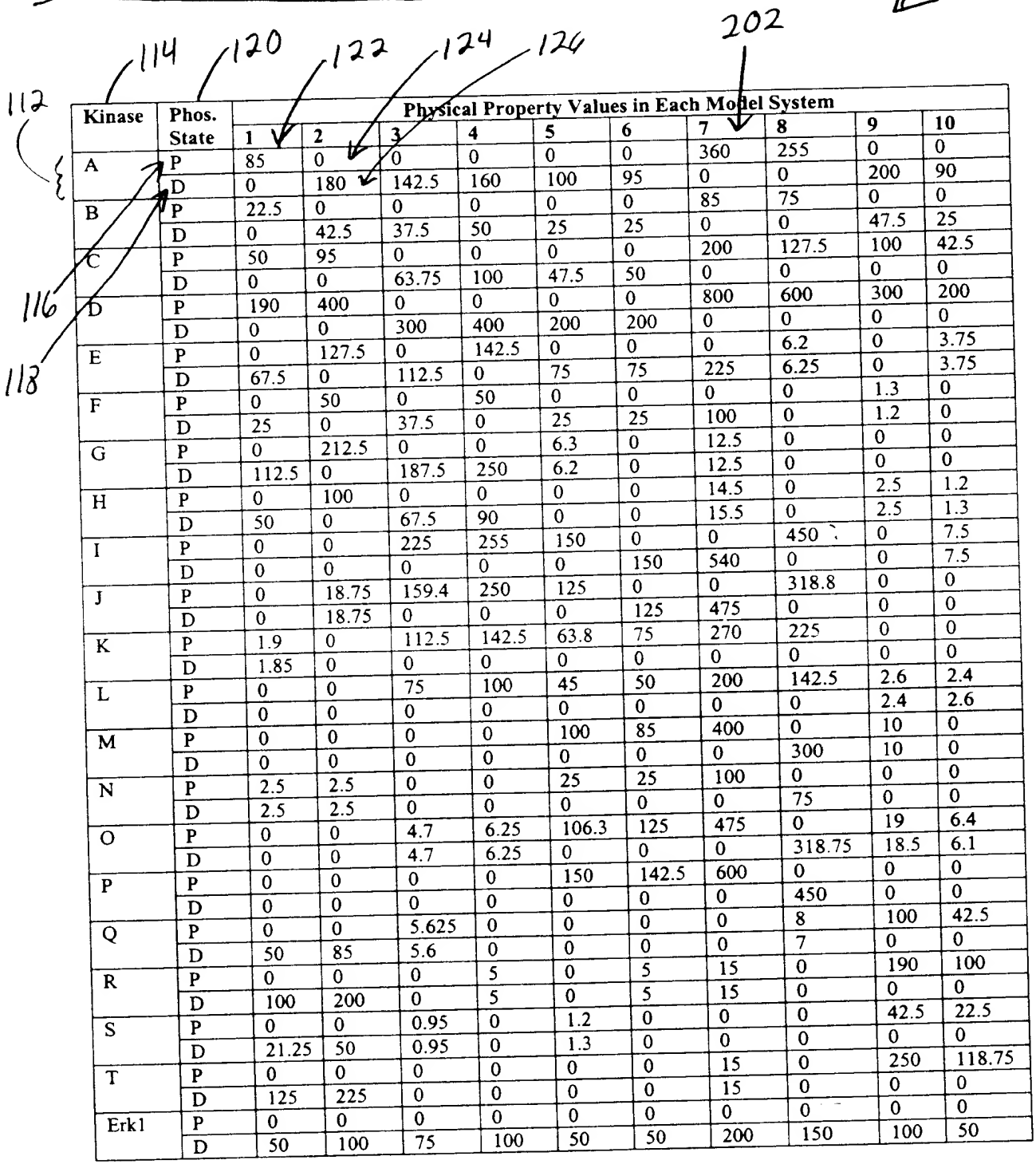


FIG. 3

INPUT DATA VALUES STORE

54



Kinase	Phos. State	Physical Property Values in Each Model System									
		1	2	3	4	5	6	7	8	9	10
A	P	85	0	0	0	0	0	360	255	0	0
	D	0	180	142.5	160	100	95	0	0	200	90
B	P	22.5	0	0	0	0	0	85	75	0	0
	D	0	42.5	37.5	50	25	25	0	0	47.5	25
C	P	50	95	0	0	0	0	200	127.5	100	42.5
	D	0	0	63.75	100	47.5	50	0	0	0	0
D	P	190	400	0	0	0	0	800	600	300	200
	D	0	0	300	400	200	200	0	0	0	0
E	P	0	127.5	0	142.5	0	0	0	6.2	0	3.75
	D	67.5	0	112.5	0	75	75	225	6.25	0	3.75
F	P	0	50	0	50	0	0	0	0	1.3	0
	D	25	0	37.5	0	25	25	100	0	1.2	0
G	P	0	212.5	0	0	6.3	0	12.5	0	0	0
	D	112.5	0	187.5	250	6.2	0	12.5	0	0	0
H	P	0	100	0	0	0	0	14.5	0	2.5	1.2
	D	50	0	67.5	90	0	0	15.5	0	2.5	1.3
I	P	0	0	225	255	150	0	0	450	0	7.5
	D	0	0	0	0	0	150	540	0	0	7.5
J	P	0	18.75	159.4	250	125	0	0	318.8	0	0
	D	0	18.75	0	0	0	125	475	0	0	0
K	P	1.9	0	112.5	142.5	63.8	75	270	225	0	0
	D	1.85	0	0	0	0	0	0	0	0	0
L	P	0	0	75	100	45	50	200	142.5	2.6	2.4
	D	0	0	0	0	0	0	0	0	2.4	2.6
M	P	0	0	0	0	100	85	400	0	10	0
	D	0	0	0	0	0	0	0	300	10	0
N	P	2.5	2.5	0	0	25	25	100	0	0	0
	D	2.5	2.5	0	0	0	0	0	75	0	0
O	P	0	0	4.7	6.25	106.3	125	475	0	19	6.4
	D	0	0	4.7	6.25	0	0	0	318.75	18.5	6.1
P	P	0	0	0	0	150	142.5	600	0	0	0
	D	0	0	0	0	0	0	0	450	0	0
Q	P	0	0	5.625	0	0	0	0	8	100	42.5
	D	50	85	5.6	0	0	0	0	7	0	0
R	P	0	0	0	5	0	5	15	0	190	100
	D	100	200	0	5	0	5	15	0	0	0
S	P	0	0	0.95	0	1.2	0	0	0	42.5	22.5
	D	21.25	50	0.95	0	1.3	0	0	0	0	0
T	P	0	0	0	0	0	0	15	0	250	118.75
	D	125	225	0	0	0	0	15	0	0	0
Erk1	P	0	0	0	0	0	0	0	0	0	0
	D	50	100	75	100	50	50	200	150	100	50

Fig. 4

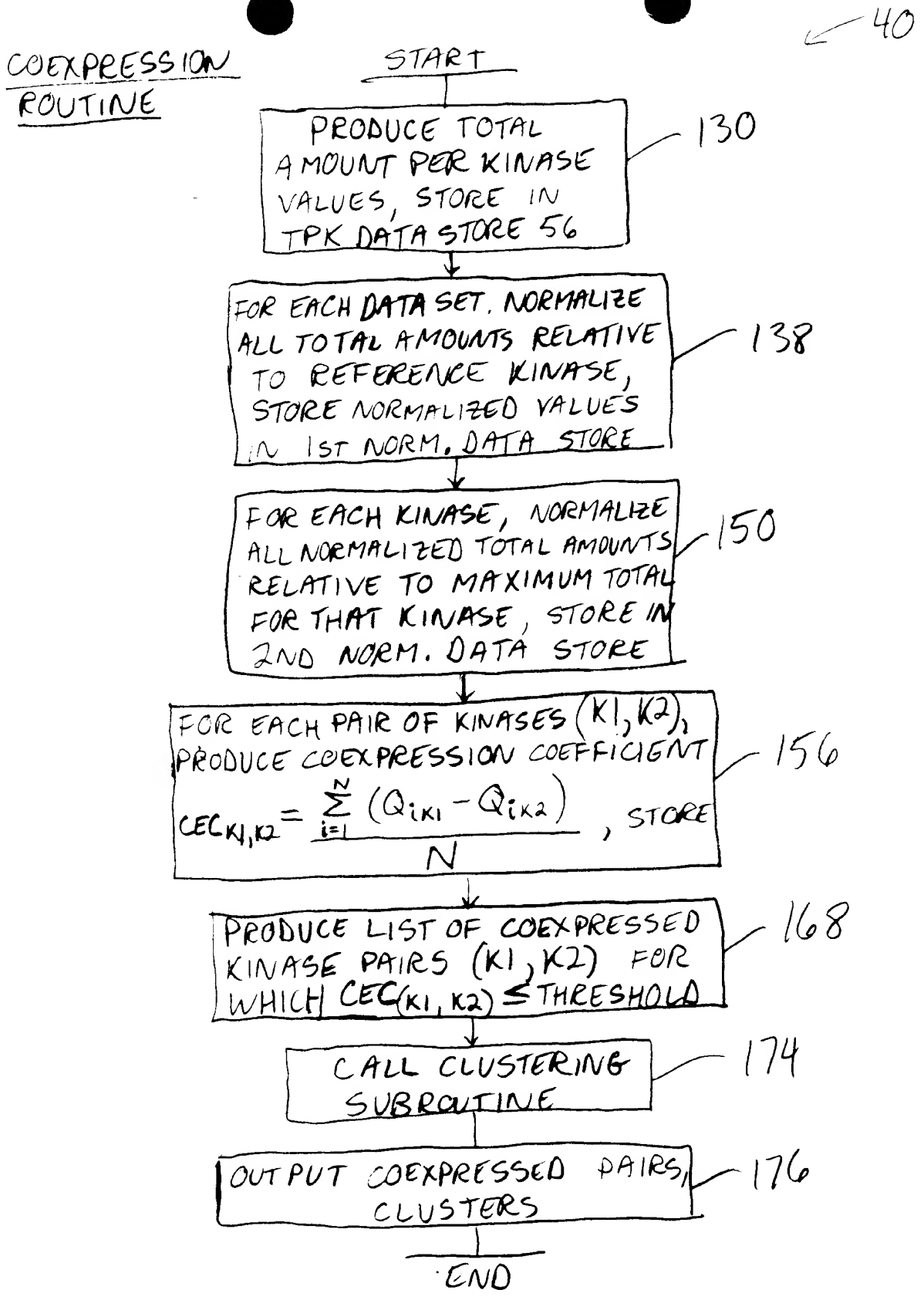

40
COEXPRESSION ROUTINE
START
PRODUCE TOTAL AMOUNT PER KINASE VALUES, STORE IN TPK DATA STORE 56
130
FOR EACH DATA SET, NORMALIZE ALL TOTAL AMOUNTS RELATIVE TO REFERENCE KINASE, STORE NORMALIZED VALUES IN 1ST NORM. DATA STORE
138
FOR EACH KINASE, NORMALIZE ALL NORMALIZED TOTAL AMOUNTS RELATIVE TO MAXIMUM TOTAL FOR THAT KINASE, STORE IN 2ND NORM. DATA STORE
150
FOR EACH PAIR OF KINASES (K1, K2), PRODUCE COEXPRESSION COEFFICIENT
$CEC_{K1,K2} = \frac{\sum_{i=1}^{N} (Q_{iK1} - Q_{iK2})}{N}$, STORE
156
PRODUCE LIST OF COEXPRESSED KINASE PAIRS (K1, K2) FOR WHICH $CEC_{(K1,K2)} \leq$ THRESHOLD
168
CALL CLUSTERING SUBROUTINE
174
OUTPUT COEXPRESSED PAIRS, CLUSTERS
176
END

FIG. 5

TOTAL PER PROTEIN (TPP) DATA STORE

140

56

System / Kinase	1 (134, 136)	2	3	4	5	6	7	8	9	10
A	85	180	142.5	160	100	95	360	255	200	90
B	22.5	42.5	37.5	50	25	25	85	75	47.5	25
C	50	95	63.75	100	47.5	50	200	127.5	100	42.5
D	190	400	300	400	200	200	800	600	300	200
E	67.5	127.5	112.5	142.5	75	75	255	11.25	0	7.5
F	25	50	37.5	50	25	25	100	0	2.5	0
G	112.5	212.5	187.5	250	12.5	0	25	0	0	0
H	50	100	67.5	90	0	0	30	0	5	2.5
I	0	0	225	255	150	150	540	450	0	15
J	0	37.5	159.4	250	125	125	475	318.8	0	0
K	3.75	0	112.5	142.5	63.8	75	270	225	0	0
L	0	0	75	100	45	50	200	142.5	5	5
M	0	0	0	0	100	85	400	300	20	0
N	5	5	0	0	25	25	100	75	0	0
O	0	0	9.4	12.5	106.3	125	475	318.75	37.5	12.5
P	0	0	0	0	150	142.5	600	450	0	0
Q	50	85	11.25	0	0	0	0	15	100	42.5
R	100	200	0	10	0	10	30	0	190	100
S	21.25	50	1.9	0	2.5	0	0	0	42.5	22.5
T	125	225	0	0	0	0	30	0	250	118.75
Erk1 (144)	50 (142)	100	75	100	50	50	200	150	100	50

132 →

FIG. 6

FIRST NORMALIZED DATA STORE 146

System / Kinase	1	2	3	4	5	6	7	8	9	10	Max value
A	170	180	190	160	200	190	180	170	200	180	200
B	45	42.5	50	50	50	50	42.5	50	47.5	50	50
C	100	95	85	100	95	100	100	85	100	85	100
D	380	400	400	400	400	400	400	400	300	400	400
E	135	127.5	150	142.5	150	150	127.5	7.5	0	15	150
F	50	50	50	50	50	50	50	0	2.5	0	50
G	225	212.5	250	250	25	0	12.5	0	0	0	250
H	100	100	90	90	0	0	15	0	5	5	100
I	0	0	300	255	300	300	270	300	0	30	300
J	0	37.5	212.5	250	250	250	237.5	212.5	0	0	250
K	7.5	0	150	142.5	127.5	150	135	150	0	0	150
L	0	0	100	100	90	100	100	95	5	10	100
M	0	0	0	0	200	170	200	200	20	0	200
N	10	5	0	0	50	50	50	50	0	0	50
O	0	0	12.5	12.5	212.5	250	237.5	212.5	37.5	25	250
P	0	0	0	0	300	285	300	300	0	0	300
Q	100	85	15	0	0	0	0	10	100	85	100
R	200	200	0	10	0	20	15	0	190	200	200
S	42.5	50	2.5	0	5	0	0	0	42.5	45	50
T	250	225	0	0	0	0	15	0	250	237.5	250

148 → 58

151

FIG. 7

SECOND NORMALIZED DATA STORE

152

System / Kinase	1	2	3	4	5	6	7	8	9	10
A	85	90	95	80	100	95	90	85	100	90
B	90	85	100	100	100	100	85	100	95	100
C	100	95	85	100	95	100	100	85	100	85
D	95	100	100	100	100	100	100	100	75	100
E	90	85	100	95	100	100	85	5	0	10
F	100	100	100	100	100	100	100	0	5	0
G	90	85	100	100	10	0	5	0	0	0
H	100	100	90	90	0	0	15	0	5	5
I	0	0	100	85	100	100	90	100	0	10
J	0	15	85	100	100	100	95	85	0	0
K	5	0	100	95	85	100	90	100	0	0
L	0	0	100	100	90	100	100	95	5	10
M	0	0	0	0	100	85	100	100	10	0
N	10	5	0	0	100	100	100	100	0	0
O	0	0	5	5	85	100	95	85	15	10
P	0	0	0	0	100	95	100	100	0	0
Q	100	85	15	0	0	0	0	10	100	85
R	100	100	0	5	0	10	7.5	0	95	100
S	85	100	5	0	10	0	0	0	85	90
T	100	90	0	0	0	0	6	0	100	95

154 → A

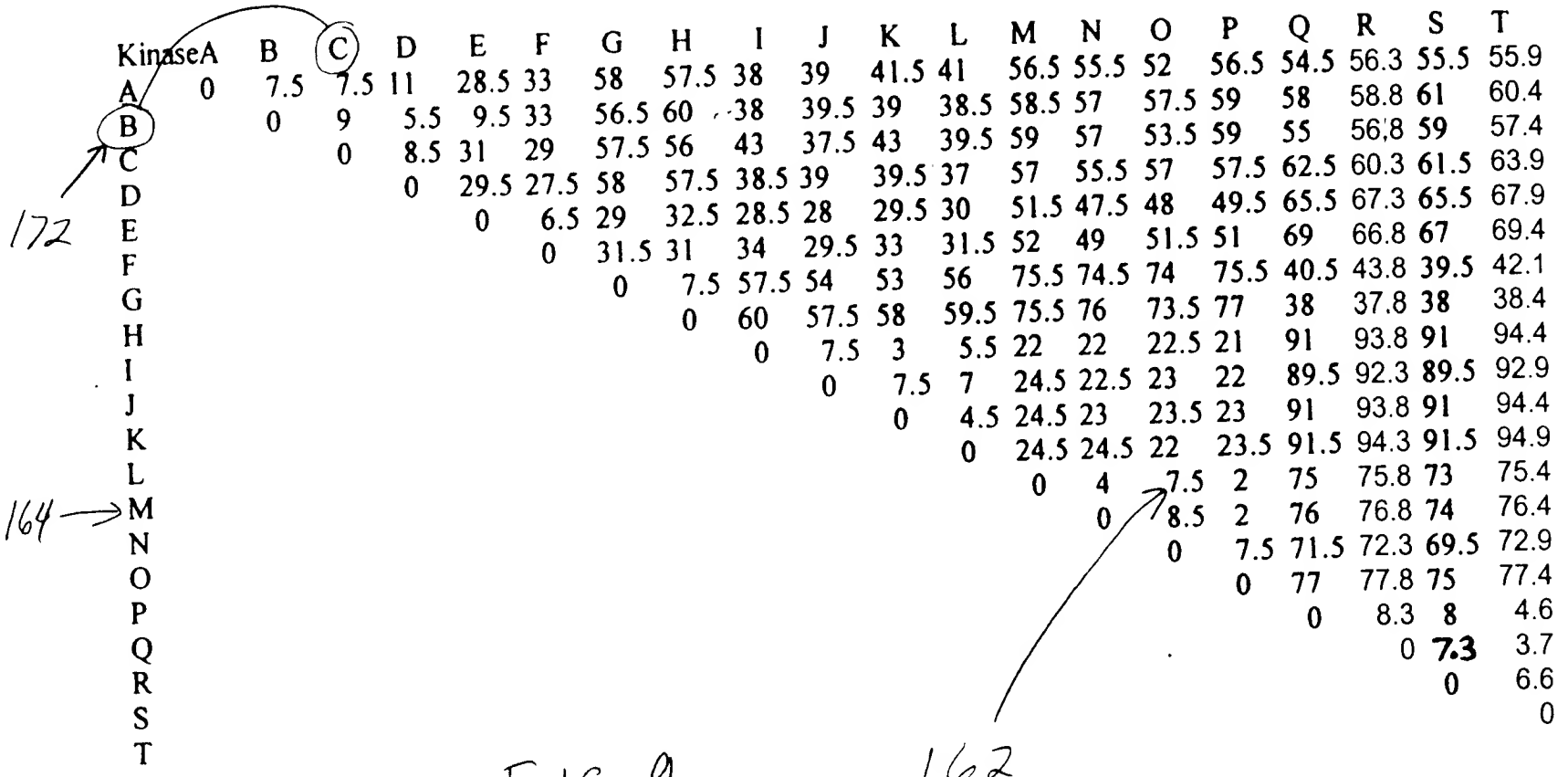
158 → M, N, O

160 ↑

60

FIG. 8

COEXPRESSION COEFFICIENTS STORE



Kinase	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T
A	0	7.5	7.5	11	28.5	33	58	57.5	38	39	41.5	41	56.5	55.5	52	56.5	54.5	56.3	55.5	55.9
B		0	9	5.5	9.5	33	56.5	60	38	39.5	39	38.5	58.5	57	57.5	59	58	58.8	61	60.4
C			0	8.5	31	29	57.5	56	43	37.5	43	39.5	59	57	53.5	59	55	56.8	59	57.4
D				0	29.5	27.5	58	57.5	38.5	39	39.5	37	57	55.5	57	57.5	62.5	60.3	61.5	63.9
E					0	6.5	29	32.5	28.5	28	29.5	30	51.5	47.5	48	49.5	65.5	67.3	65.5	67.9
F						0	31.5	31	34	29.5	33	31.5	52	49	51.5	51	69	66.8	67	69.4
G							0	7.5	57.5	54	53	56	75.5	74.5	74	75.5	40.5	43.8	39.5	42.1
H								0	60	57.5	58	59.5	75.5	76	73.5	77	38	37.8	38	38.4
I									0	7.5	3	5.5	22	22	22.5	21	91	93.8	91	94.4
J										0	7.5	7	24.5	22.5	23	22	89.5	92.3	89.5	92.9
K											0	4.5	24.5	23	23.5	23	91	93.8	91	94.4
L												0	24.5	24.5	22	23.5	91.5	94.3	91.5	94.9
M													0	4	7.5	2	75	75.8	73	75.4
N														0	8.5	2	76	76.8	74	76.4
O															0	7.5	71.5	72.3	69.5	72.9
P																0	77	77.8	75	77.4
Q																	0	8.3	8	4.6
R																		0	7.3	3.7
S																			0	6.6
T																				0

172

164

166

162

62

FIG. 9

170

A+B, A+C, A+D
B+C, B+D, B+E
C+D
E+F
G+H
I+K, I+L, I+J
J+K, J+L
K+L
M+N, M+O, M+P
N+O, N+P
O+P
Q+R, Q+S, Q+T
R+S, R+T
S+T

64

COEXPRESSED PAIRS STORE

FIG. 10

COEXPRESSED CLUSTERS STORE

66

188 →
1. A+B, A+C, A+D, B+C, B+D, C+D
2. J+K, J+L, K+L, I+J, I+K, I+L
3. M+N, M+O, M+P, N+O, N+P, O+P
4. Q+R, Q+S, Q+T, R+S, R+T, S+T

FIG. 11

CLUSTERING SUBROUTINE

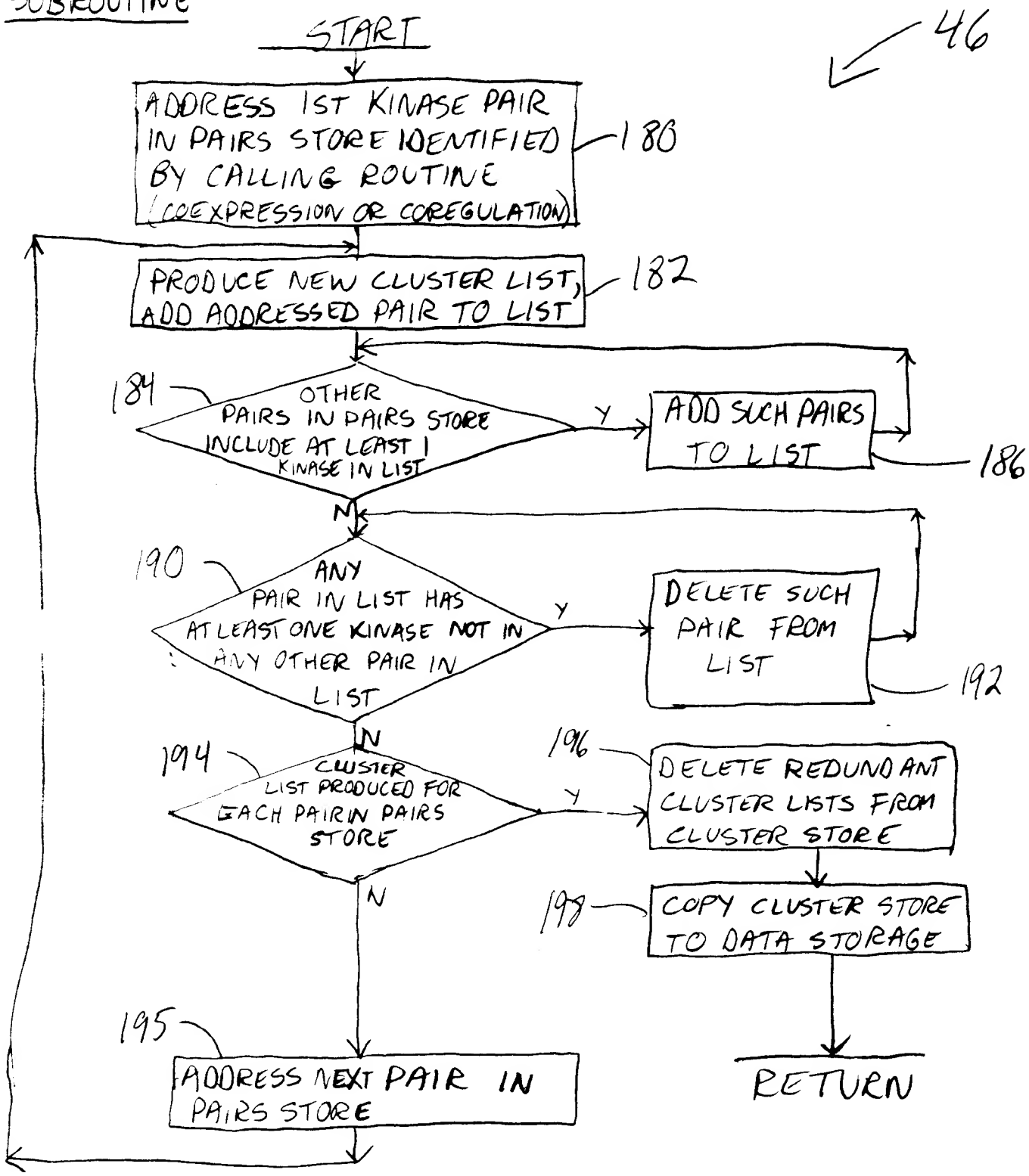


FIG. 12

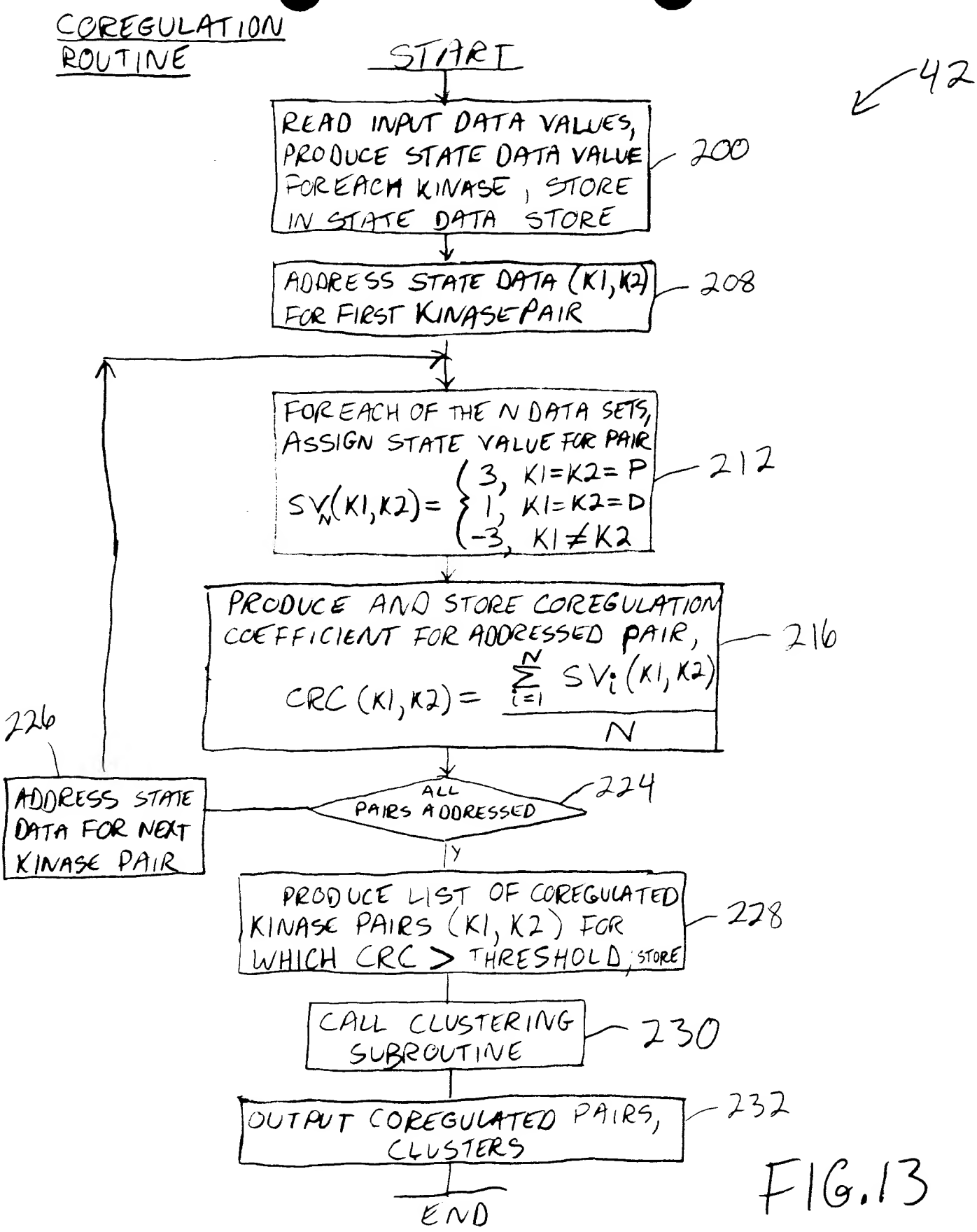

COREGULATION ROUTINE
START
42
READ INPUT DATA VALUES, PRODUCE STATE DATA VALUE FOR EACH KINASE, STORE IN STATE DATA STORE
200
ADDRESS STATE DATA (K1, K2) FOR FIRST KINASE PAIR
208
FOR EACH OF THE N DATA SETS, ASSIGN STATE VALUE FOR PAIR
$SV_N(K1,K2) = \begin{cases} 3, & K1=K2=P \\ 1, & K1=K2=D \\ -3, & K1 \neq K2 \end{cases}$
212
PRODUCE AND STORE COREGULATION COEFFICIENT FOR ADDRESSED PAIR,
$CRC(K1,K2) = \frac{\sum_{i=1}^{N} SV_i(K1,K2)}{N}$
216
ALL PAIRS ADDRESSED
224
N
Y
226
ADDRESS STATE DATA FOR NEXT KINASE PAIR
PRODUCE LIST OF COREGULATED KINASE PAIRS (K1, K2) FOR WHICH CRC > THRESHOLD, STORE
228
CALL CLUSTERING SUBROUTINE
230
OUTPUT COREGULATED PAIRS, CLUSTERS
232
END

FIG. 13

STATE DATA STORE

214

204

61

System Kinase	1	2	3	4	5	6	7	8	9	10
A	P	D	D	D	D	D	P	P	D	D
B	P	D	D	D	D	D	P	P	D	D
C	P	P	D	D	D	D	P	P	P	P
D	P	P	D	D	D	D	P	P	P	P
E	D	P	D	P	D	D	D	N.S.	N.S.	N.S.
F	D	P	D	P	D	D	D	N.S.	N.S.	N.S.
G	D	P	D	D	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
H	D	P	D	D	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
I	N.S.	N.S.	P	P	P	D	D	P	N.S.	N.S.
J	N.S.	N.S.	P	P	P	D	D	P	N.S.	N.S.
K	N.S.	N.S.	P	P	P	P	P	P	N.S.	N.S.
L	N.S.	N.S.	P	P	P	P	P	P	N.S.	N.S.
M	N.S.	N.S.	N.S.	N.S.	P	P	P	D	N.S.	N.S.
N	N.S.	N.S.	N.S.	N.S.	P	P	P	D	N.S.	N.S.
O	N.S.	N.S.	N.S.	N.S.	P	P	P	D	N.S.	N.S.
P	N.S.	N.S.	N.S.	N.S.	P	P	P	D	N.S.	N.S.
Q	D	D	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	P	P
R	D	D	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	P	P
S	D	D	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	P	P
T	D	D	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	P	P

206 →

210

FIG. 14

COREGULATION COEFFICIENTS STORE

Kinase	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T
A	0	1.6	0.4	0.4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
B		0	0.4	0.4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
C			0	2.2	0	0	0.5	0.5	0	0	0	0	0	0	0	0	0	0	0	0
D				0	0	0	0.5	0.5	0	0	0	0	0	0	0	0	0	0	0	0
E					0	1.57	0.5	0.5	0	0	0	0	0	0	0	0	0	0	0	0
F						0	0.5	0.5	0	0	0	0	0	0	0	0	0	0	0	0
G							0	1.5	0	0	0	0	0	0	0	0	0	0	0	0
H								0	0	0	0	0	0	0	0	0	0	0	0	0
I									0	2.33	1.0	1.0	0	0	0	0	0	0	0	0
J										0	1.0	1.0	0	0	0	0	0	0	0	0
K											0	3.0	1.5	1.5	1.5	1.5	0	0	0	0
L												0	1.5	1.5	1.5	1.5	0	0	0	0
M													0	2.5	2.5	2.5	0	0	0	0
N														0	2.5	2.5	0	0	0	0
O															0	2.5	0	0	0	0
P																0	0	0	0	0
Q																	0	2.0	2.0	2.0
R																		0	2.0	2.0
S																			0	2.0
T																				0

220 → (row A)

218 (B–C)

↑ 222

68 ↗

FIG. 15

COREGULATED PAIRS

70

A+B, A+C, A+D
B+C, B+D
C+D, C+G, C+H
D+G, D+H
E+F, E+G, E+H
F+G, F+H
G+H
I+J , I+K, I+L
J+K, J+L
K+L, K+M, K+N, K+O, K+P
L+M, L+N, L+O, L+P
M+N, M+O, M+P
N+O, N+P
O+P
Q+R, Q+S, Q+T
R+S, R+T
S+T

FIG. 16

COREGULATED CLUSTERS

1. A+B, A+C, A+D, B+C, B+D, C+D, C+G, C+H, D+G, D+H, E+F, E+G, E+H, F+G, F+H, G+H,
2. I+J, I+K, I+L , J+K, J+L, K+L, K+M, K+N, K+O, K+P, M+N, M+O, M+P, N+O, N+P, O+P
3. Q+R, Q+S, Q+T, R+S, R+T, S+T

72

FIG. 17

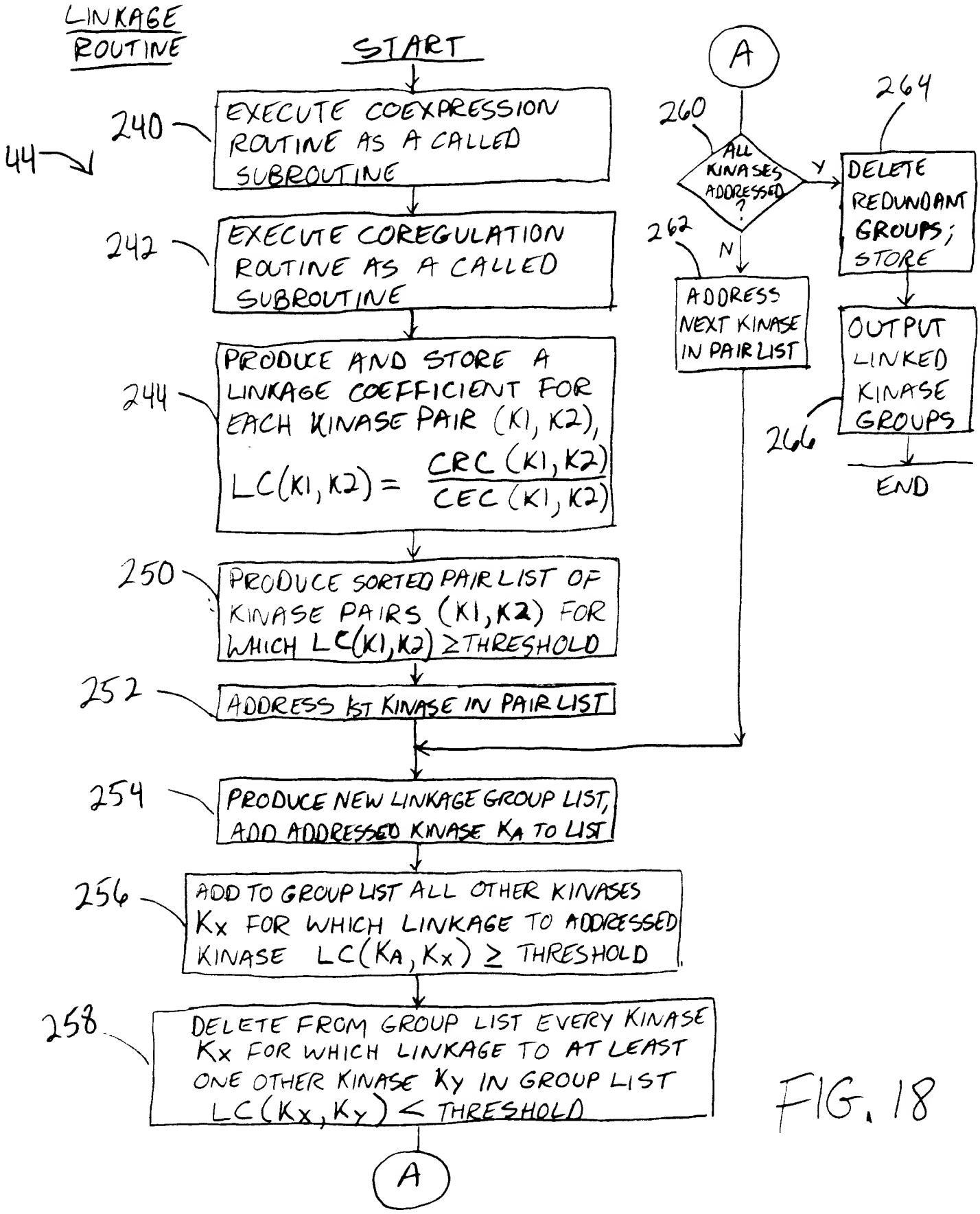

LINKAGE ROUTINE
START
44
240
EXECUTE COEXPRESSION ROUTINE AS A CALLED SUBROUTINE
242
EXECUTE COREGULATION ROUTINE AS A CALLED SUBROUTINE
244
PRODUCE AND STORE A LINKAGE COEFFICIENT FOR EACH KINASE PAIR (K1, K2),
LC(K1, K2) = CRC (K1, K2) / CEC (K1, K2)
250
PRODUCE SORTED PAIR LIST OF KINASE PAIRS (K1, K2) FOR WHICH LC(K1, K2) ≥ THRESHOLD
252
ADDRESS 1ST KINASE IN PAIR LIST
254
PRODUCE NEW LINKAGE GROUP LIST, ADD ADDRESSED KINASE KA TO LIST
256
ADD TO GROUP LIST ALL OTHER KINASES Kx FOR WHICH LINKAGE TO ADDRESSED KINASE LC(KA, Kx) ≥ THRESHOLD
258
DELETE FROM GROUP LIST EVERY KINASE Kx FOR WHICH LINKAGE TO AT LEAST ONE OTHER KINASE Ky IN GROUP LIST LC(Kx, Ky) < THRESHOLD
A
A
260
ALL KINASES ADDRESSED ?
Y
N
262
ADDRESS NEXT KINASE IN PAIR LIST
264
DELETE REDUNDANT GROUPS; STORE
266
OUTPUT LINKED KINASE GROUPS
END

FIG. 18

LINKAGE COEFFICIENTS STORE

74

248 →

Kinase	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T
A	0	21.3	5.3	3.6	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
B		0	4.4	7.3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
C			0	25.9	0	0	0.9	0.9	0	0	0	0	0	0	0	0	0	0	0	0
D				0	0	0	0.9	0.9	0	0	0	0	0	0	0	0	0	0	0	0
E					0	24.2	1.7	1.5	0	0	0	0	0	0	0	0	0	0	0	0
F						0	1.6	1.6	0	0	0	0	0	0	0	0	0	0	0	0
G							0	20	0	0	0	0	0	0	0	0	0	0	0	0
H								0	0	0	0	0	0	0	0	0	0	0	0	0
I									0	31.1	33.3	18.2	0	0	0	0	0	0	0	0
J										0	13.3	14.3	0	0	0	0	0	0	0	0
K											0	66.7	6.1	6.5	6.4	6.5	0	0	0	0
L												0	6.1	6.1	6.8	6.4	0	0	0	0
M													0	62.5	33.3	125	0	0	0	0
N														0	29.4	125	0	0	0	0
O															0	33.3	0	0	0	0
P																0	0	0	0	0
Q																	0	24.1	25	43.5
R																		0	27.4	54.1
S																			0	30.3
T																				0

246

249 ↑

FIG. 19

Pair Number	Linkage Coefficient	Kinase Pair
1	125	M, P
2	125	N, P
3	66.7	K, L
4	62.5	M, N
5	54.1	R, T
6	43.5	Q, T
7	33.3	I, K
8	33.3	M, O
9	33.3	O, P
10	31.1	I, J
11	30.3	S, T
12	29.4	N, O
13	27.4	R, S
14	25.9	C, D
15	25	Q, S
16	24.2	E, F
17	24.1	Q, R
18	21.3	A, B
19	20	G, H
20	18.2	I, L
21	14.3	J, L
22	13.3	J, K
23	7.3	B, D
24	6.8	L, O
25	6.5	K, N
26	6.5	K, P
27	6.4	K, O
28	6.4	L, P
29	6.1	K, M
30	6.1	L, M
31	6.1	L, N
32	5.3	A, C
33	4.4	B, C
34	3.6	A, D
35	1.7	E, G
36	1.6	F, G
37	1.6	F, H
38	1.5	E, H
39	0.9	C, G
40	0.9	C, H
41	0.9	D, G
42	0.9	D, H

76

Fig. 20

1. A, B, C, D

257 → 2. C, D, G, H

3. E, F, G, H

4. I, J, K, L

5. K, L, M, N, O, P

6. Q, R, S, T

Fig. 21